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Blandamer, Michael J.; Briggs, Barbara; Cullis, Paul M.; Kirby, Stuart D.; Engberts, Jan B.F.N.

Published in:
Journal of the Chemical Society%2C Faraday Transactions

DOI:
[10.1039/a605373d](https://doi.org/10.1039/a605373d)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
1997

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Blandamer, M. J., Briggs, B., Cullis, P. M., Kirby, S. D., & Engberts, J. B. F. N. (1997). Reorganisation of alkyl chains in vesicles formed in aqueous solution by dialkyldimethylammonium bromide, $R_2N^+Me_2Br^-$ where $R = C_{12}H_{25}$, $C_{14}H_{29}$, $C_{16}H_{33}$ or $C_{18}H_{37}$. *Journal of the Chemical Society%2C Faraday Transactions*, 93(3). <https://doi.org/10.1039/a605373d>

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Reorganisation of alkyl chains in vesicles formed in aqueous solution by dialkyldimethylammonium bromide, $R_2N^+Me_2Br^-$ where $R = C_{12}H_{25}$, $C_{14}H_{29}$, $C_{16}H_{33}$ or $C_{18}H_{37}$

Michael J. Blandamer,^{*a} Barbara Briggs,^a Paul M. Cullis,^a Stuart D. Kirby^a and Jan B. F. N. Engberts^b

^a Department of Chemistry, The University of Leicester, University Road, Leicester, UK LE1 7RH,

^b Department of Organic and Molecular Inorganic Chemistry, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands

Differential scanning calorimetry (DSC) scans are reported for aqueous solutions containing vesicles formed by four dialkyldimethylammonium bromides; $R_2N^+Me_2Br^-$ where $R =$ dodecyl (DDAB), tetradecyl (DTAB), hexadecyl (DHAB) or octadecyl (DOAB). Electron micrographs of DTAB (aq; 2×10^{-3} mol dm⁻³) confirmed that these solutions, prepared at 50 °C, contain vesicles, with radii *ca.* 700 nm. DSC scans of these solutions, initially cooled to 5 °C and then scanned with increasing temperature, showed no evidence of an extremum in isobaric heat capacity as a function of temperature, associated with a chain-packing transition in the vesicular bilayer at a characteristic temperature, T_m . However, clear evidence for such a transition near 29 °C was obtained after this solution had been held at 5 °C for periods up to 11 h. With increase in the time during which the DTAB solution was held at 5 °C, the recorded signal associated with the melting temperature increased in intensity. However, there was again no evidence for this transition if the solution was cooled to 5 °C and the heat capacity dependence on temperature immediately re-scanned. The patterns are discussed in terms of a kinetic control, *during cooling*, of the packing of dialkyl chains in the bilayers.

A similar pattern was observed for DDAB (aq) where $T_m = 15.8$ °C. In the case of DHAB (aq) where $T_m = 28.1$ °C, no kinetic features were apparent using DSC to study the gel to chain-packing transition.

Using DSC, a chain-packing transition can be characterised for vesicles formed by (sodium) dialkylphosphates and di-*n*-alkyldimethylammonium bromides.¹ Three important parameters describe these transitions; (i) the transition or melting temperature T_m , (ii) the patch number describing the number of monomers in the bilayer undergoing the cooperative transition, and (iii) the enthalpy of fusion per monomer. In this connection we have shown that the protocol for preparation of vesicular solutions is critical if reproducible results are to be obtained. Consequently, we have recommended that, in the case of DSC experiments using a sensitive microcalorimeter, the 'hot water' method should be used.^{2,3}

In our previously reported DSC-based studies on vesicular systems (for further references see ref. 1) the transition^{4,5} for a given system was monitored as the temperature of the sample (volume 1.2 cm³) was slowly increased.⁶ When the temperature of the sample was *ca.* 20 °C above T_m (but not above 90 °C), heating of the sample was stopped and the sample was allowed to cool in the calorimeter. The sample was cooled to at least 20 °C below T_m (but not below 5 °C). The solution was held at the low temperature for periods up to 11 h before the sample was reheated. For a series of dialkylphosphates^{2,3,7} and for dimethyldioctadecylammonium bromide⁶ (DOAB) the same scan pattern was recorded in each case. We concluded, therefore, that, in the case of vesicles formed by DOAB and by dialkylphosphates, the fact that the scans were reproducible and repeatable meant that the calorimeter was tracking the equilibrium properties of these vesicular solutions. In other words, the recorded transitions are reversible in the thermodynamic sense. Exceptions to this generalisation concerned instances where ethanol was added to aqueous vesicular systems. Reversibility was not observed; a feature attributed to the kinetics of incorporation of ethanol into the bilayers.³

Here we report evidence, from DSC, of kinetic control on

the chain-packing transition when the vesicular aqueous systems containing vesicles produced by two di-*n*-alkyldimethylammonium bromides are cooled. A time-dependence for the shape of recorded scans has been reported⁸ for the phase transition in bilayers formed by saturated diacylphosphatidylcholines (DC₁₆PC) in systems containing lindane, but in this case the kinetic features are linked to the temperature dependence of the partition coefficient for lindane into the bilayers.

Experimental

The di-*n*-alkyldimethylammonium bromides used in this study: di-*n*-dodecyldimethylammonium bromide (DDAB), dimethyldi-*n*-tetradecylammonium bromide (DTAB), di-*n*-hexadecyldimethylammonium bromide (DHAB) and DOAB, were purchased from Aldrich Chemical Co. and were used as supplied. The appropriate mass of monomer was added to water and heated to *ca.* 50 °C for 30 min with vigorous stirring.

A MicroCal DSC was used as previously described.⁶

Electron micrographs of vesicle solutions were obtained as previously described.⁹

Results

The patterns observed using the DSC for DDAB and DTAB were very similar so we concentrate attention on the results for vesicular systems prepared using DTAB.

Electron micrographs for DTAB [2×10^{-3} (monomer mol) dm⁻³] confirmed that, under these conditions, this surfactant forms vesicles, Fig. 1. The micrograph was supplied by the Electron Microscope Laboratory at the University of Leicester and was obtained several hours after the vesicle system

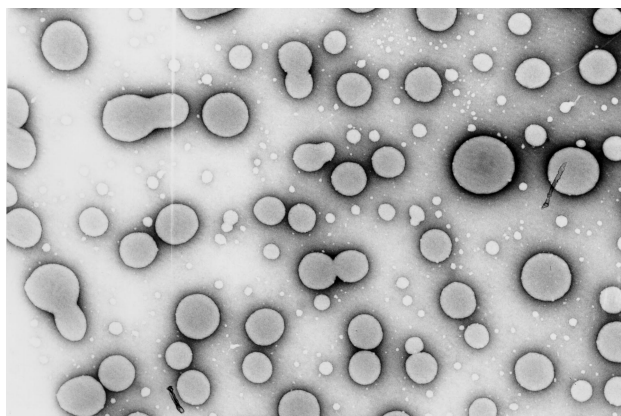


Fig. 1 Electronmicrograph of vesicles in an aqueous system¹⁰ produced by DTAB [aq; 2×10^{-2} (monomer mol) dm^{-3}]; magnification = 1.9×10^4 .

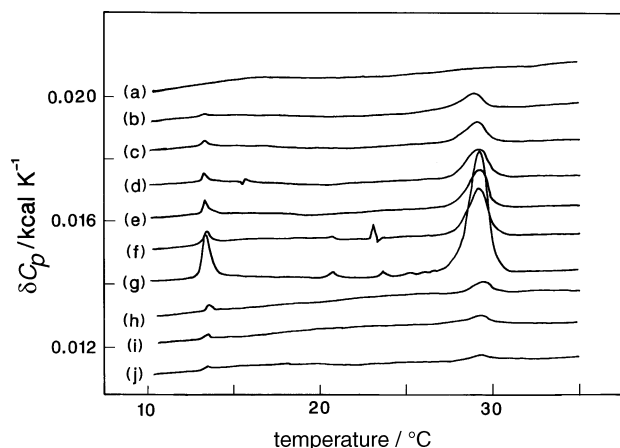


Fig. 2 Dependence on temperature of the differential heat capacities (reference, water) for aqueous systems containing DTAB [aq; 2×10^{-3} (monomer mol) dm^{-3}]. Scans recorded (a) for freshly prepared solutions and for solutions which had been scanned to 35°C, cooled to 5°C and held at 5°C for (b) 1, (c) 2, (d) 3, (e) 4, (f) 5 and (g) 11 h. For (h), (i) and (j), the samples were heated as soon as each sample had been cooled to 5°C. The scans have been displaced on the heat capacity axis for clarity.

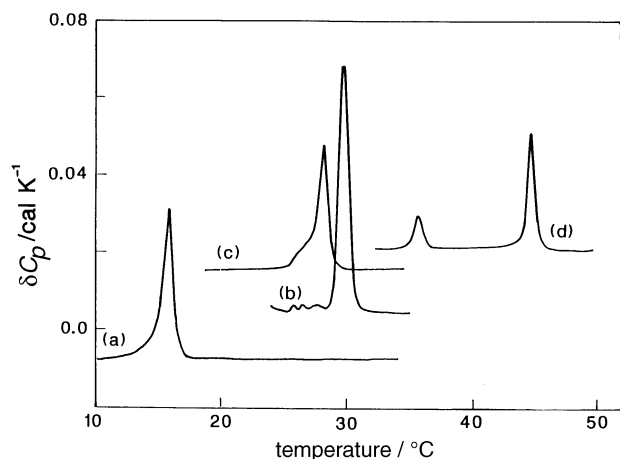


Fig. 3 Dependence on temperature of the differential heat capacities (reference, water) for aqueous systems containing dialkyl-dimethyl-ammonium bromide vesicles; (a) DDAB [aq; 2×10^{-2} (monomer mol) dm^{-3}] after being held at 5°C for 6 h (b) DTAB [aq; 2×10^{-2} (monomer mol) dm^{-3}] after being held at 5°C for 7 h, (c) DHAB [aq; 2×10^{-3} (monomer mol) dm^{-3}] and (d) DOAB [aq; 2×10^{-3} (monomer mol) dm^{-3}], with immediate scanning after cooling to 5°C.

had been prepared in the Department of Chemistry. It is important to note that the micrograph was obtained after negative staining with uranyl acetate solution, the water having been removed by evaporation from the aqueous vesicular system. Notwithstanding these problems associated with this technique, the evidence is clear-cut for vesicles in the system. In the system recorded in Fig. 1, the diameters of the vesicles are *ca.* 700 nm. We make these points to set into context the fact that no extremum was recorded by the DSC when a freshly prepared vesicular solution was used, Fig. 2(a). However, when the vesicular system was cooled to 5°C and held at this temperature for 1 h, the new scan showed a small extremum at 29.3°C, Fig. 2(b). The latter procedure was repeated, except that the time over which the vesicular system was held at the lower temperature was gradually increased, Fig. 2(b)–(f). The intensity of the extremum at 29.3°C increased, with evidence of a much smaller extremum near 14°C. When the solution had been held at 5°C for 11 h [Fig. 2(g)] the extrema at 29.3 and 14°C were fully developed. Significantly, when the latter system having reached 35°C was cooled to 5°C and then immediately re-scanned, the extrema had almost disappeared [Fig. 2(h)]. Indeed, when this system was cooled and re-scanned with no time delay at 5°C, only slight evidence of the two extrema was seen in the trace [Fig. 2(i) and (j)].

A solution held at 5°C for 11 h was heated to just below 29.3°C (*i.e.* below T_m), recooled to 5°C and then immediately scanned to above 29.3°C. The DSC scan showed the same extremum at 29.3°C as recorded in Fig. 2(g).

The DSC results for DTAB solutions containing 1×10^{-2} (mol monomer) dm^{-3} showed a similar pattern except that the extremum was fully developed after the sample was held at 5°C for only 6 h. Again, when such a solution having been heated to above T_m and cooled to 5°C, was immediately re-scanned the intensity of the extremum at 29°C was much reduced. With increase in concentration of DTAB to 2×10^{-2} (mol monomer) dm^{-3} , extrema at 29.3 and 14°C were recorded, even where the solution was re-scanned after cooling to 5°C although the intensity of, for example, the signal at 29°C was much reduced, *cf.* Fig. 2(g). In the case of DDAB, electron micrographs of a solution prepared at a concentration of 2×10^{-2} showed clear evidence of vesicle formation (data not shown) although this conclusion is tempered with the same reservations expressed above with respect to Fig. 1. The scan recorded by the DSC for freshly prepared solutions showed no extremum. Similarly, scans for the same solution recorded immediately on cooling to 5°C showed very weak extrema. Again, just as for DTAB, an extremum in the scan was recorded at 15.8°C when the solution had been held at 5°C for, in this case, 6 h. When this solution was cooled to 5°C and immediately re-scanned no extremum was recorded.

The complicated time-dependent patterns recorded for DTAB and DDAB were not observed for DHAB. The DSC scan for freshly prepared DHAB [2×10^{-3} (monomer mol) dm^{-3}] showed an intense signal with a maximum at 28.1°C. The solutions were cooled to 5°C and the DSC scan immediately recorded. The resulting scan was identical, as was the scan recorded after holding the solution at 5°C for 7 h. A summary of the DSC scans for four systems is shown in Fig. 3. Overall, T_m increases with increase in alkyl chain length⁹ but DTAB and DHAB show an inversion in order near 30°C.

Discussion

Micelle formation, lipid bilayer formation and vesicle formation are examples of spontaneous self-organising systems, usually in aqueous solution. Similarly, when the concentration of monomer falls below the c.m.c. in the case of, for example, ionic surfactants the micelles spontaneously deaggregate.¹⁰ The relaxation times associated with formation and deaggre-

gation of ionic micelles are generally in the microsecond range.^{11–13} Although rates of vesicle formation by dialkylphosphates and by dialkyldimethylammonium bromides have not been measured, the previously reported DSC data for these systems² support the contention that self-assembly is rapid and that the vesicles are thermally stable. That is to say, other than the chain-packing transition, the vesicles do not break up, at least at temperatures over a reasonable range above T_m . Certainly, this argument is supported by the DSC results for DOAB(aq) and DHAB(aq). Thus T_m increases with increase in chain length, a pattern consistent with that observed for the dialkylphosphates.²

An important feature concerning the DSC scans for vesicles formed from mixtures of dialkylphosphates is the extent to which the dialkyl chains fit together in the bilayer systems.⁷ Nevertheless, this aspect of the problem was only considered in the context of the patterns formed in the DSC plots.⁷ The observation that there is a kinetic component to the DSC scans recorded in the case of DDAB and DTAB can most easily be explained in terms of similar packing requirements involved in the formation of the bilayers which, in these cases, is slow at 5 °C. The alternative possibility that, at high temperatures (above the chain-repacking temperature for a given system) the vesicles deaggregated, seems less likely. In this case, the time dependence would be associated with the rate of vesicle formation from the monomeric cations in solution. However, as commented above, all evidence points to rates of aggregation which are considerably faster than indicated by the timescales associated with these DSC data, Fig. 2. The kinetic features observed here are associated with the relatively rapid cooling of the system where the bilayers are in the disordered form. A likely explanation is in terms of a supercooling of the bilayer leading to a metastable state at 5 °C. If this was the case, the repeat scans would show either no, or only partially developed, extrema. The tendency to recover fully developed extrema over a period of time shows that the organisation of the disordered state into the ordered state is not instantaneous. An otherwise smooth equilibrium transformation from the high-temperature disordered to low-temperature ordered configurations within the bilayer at a single characteristic temperature requires cooperative ordering within domains of several hundred alkyl chains.¹ Clearly the difference in local order between ordered and disordered configurations is more marked in the case of shorter alkyl chains. Hence the necessary nucleation has a longer half-life.

The results, particularly for DDAB and DTAB, provide, as far as we are aware, convincing evidence for kinetic control of the ordered state. It is remarkable that this evidence emerges

from DSC experiments which are normally linked to a scanning of equilibrium states. It is also noteworthy that, based on the results of scans using freshly prepared solutions, the initial conclusion was that DDAB and DTAB either did not form vesicles or these were in the disordered state throughout this temperature range. The electron microscopy evidence prompted a closer examination of the thermal properties revealed by DSC, and led to the uncovering of these remarkably slow kinetic processes.

We thank EPSRC for their support under the Molecular Recognition Initiative (MRI) and the Royal Society for their support.

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Paper 6/05373D; Received 31st July, 1996